REMARKS

Upon entry of the instant amendment, claims 2, 7, 8, 10-45, constitute the pending claims in the present application. Claims 1, 3-6, 9, 46-69 are canceled without prejudice. Applicants reserve the right to prosecute claims of similar or identical scope in future applications.

Applicants note that the drawings filed on March 18, 2002 are accepted by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Specification objections

The Office Action objects to the specification because certain trademarks, such as AFFIBODY, TRINECTIN and ANTICALIN were used without capitalization and accompanying generic terminologies. In addition, the Office Action also points out that page 25, lines 4-8 incorporates by reference a U.S. Patent Application, but does not provide serial number. The Office Action requests correction of these defects.

Accordingly, Applicants have amended the specification to correct these typographical errors. Applicants have also added generic descriptions for the products represented by these trademark names, based on the description by the respective trademark owners, and the commonly known characteristics of the products with these trademarks. Applicants submit that such amendments are not new matters, since they merely supplement the characteristics inherent to the products under the respective trademarks. Reconsideration and withdrawal of the objection are respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph – written description

Claims 1-3, 5-8, and 10-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action

raised several issues purportedly related to the Written Description requirement, which Applicants will address below.

The case cited by the Office Action, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, has a brief review of the history of the written description requirement (935 F.2d 1555, 1560-2):

> "[w]ritten description" requirement most often comes into play where claims not presented in the application when filed are presented thereafter... The question raised by these situations is most often phrased as whether the application provides "adequate support" for the claim(s) at issue; it has also been analyzed in terms of "new matter" under 35 U.S.C. § 132.
>
> ...
>
> To the uninitiated, it may seem anomalous that the first paragraph of 35 U.S.C. § 112 has been interpreted as requiring a separate "description of the invention," when the invention is, necessarily, the subject matter defined in the claims under consideration. ... One may wonder what purpose a separate "written description" requirement serves, when the second paragraph of § 112 expressly requires that the applicant conclude his specification "with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."
>
> One explanation is historical: the "written description" requirement was a part of the patent statutes at a time before claims were required. ...The patent laws then in effect, namely the Patent Act of 1793, did not require claims...
>
> ...
>
> Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.

Therefore, MPEP 2163.03 stresses that "rejection of an original claim for lack of written description should be rare." In addition, the final guidelines for 35 U.S.C. 112 points out that there is a strong presumption that the specification as filed provides adequate written description support for the claimed invention. It is under this context that the following language in MPEP 2163.02 (8th edition released in August, 2001) could be properly understood: "Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." (emphasis added). A disclosure as filed is *prima facie* adequate.

Evidently, the purpose of the written description requirement is mainly to ensure that there is no new matter introduced by Applicants during later prosecution efforts. Id. at 1560.

That is the reason why "rejection of an original claim for lack of written description should be rare," since "the invention is, necessarily, the subject matter defined in the claims under consideration." Id. Therefore, original claims of the pending invention presumably have met the written description requirement. Applicants submit that amendments to claim 2 and some of its dependent claims are merely grammatical changes for clarification purposes, and thus should not change their status as "original claims" for the purpose of written description requirement.

The Office Action cited page 2 of the specification, in support of its argument that the examples in the art do not adequately describe the genus of molecules having the property of a molecular clasp. In view of the written description requirement background and guideline discussed above, Applicants submit that none of the references discussed in the "Background" section of the instant specification broadly describe the concept of modular molecular clasp as described in the instant specification, including the original claims, the many figures, and the texts detailing the different embodiments of the claimed invention (see, for example, the "Summary of the Invention" section).

In addition, since independent claims 1 and 3-6 are canceled to expedite prosecution, Applicants only need to address the adequacy of description for the still pending independent claim 2 and its dependent claims. For the same reason above, Applicants submit that the texts, figures, examples and original claims of the instant application provides sufficient written description for the subject matter now claimed.

Next, the Office Action alleges that "adequate description of the molecular clasp must teach the skilled artisan how any molecule capable of binding a ligand,...can be configured together such that the allosteric alteration of the of the [sic] molecular clasp is facilitated by the transducer in response to ligand binding to said molecular recognition element, producing a detectable change in an activity of said effector." The Office Action seems to be concerned about the detailed mechanism of how the claimed molecular clasp works, because "the functional characteristics of an assemblage of a molecular recognition element, a transducer and an effector molecule are highly unpredictable."

Applicants submit that a description of the structure of the claimed invention, coupled with a functional characteristic is sufficient to satisfy the written description requirement. In contract, Applicants submit that there is no requirement for the Applicants to describe the

detailed mechanism of how an invention works, which seems to be the main concern of the Office Action here. *See Parker v. Frilette*, 462 F.2d 544, 547 (CCPA 1972) ("[an] inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice") (MPEP 2138.05). In fact, 35 U.S.C. 112, first paragraph requires Applicants to adequately describe how to "make and use" the claimed invention, not to explain how the claimed invention works. A skilled artisan need not know the mechanism as to how the assemblage of MRE, transducer and effector work together to "make" the claimed modular molecular clasp – the following section responding to the enablement rejection describes in detail why this is so. But briefly to recap the main points, Applicants submit that the preferred random mutagenesis coupled with screening for desired function would provide a skilled artisan a powerful tool to "make" many claimed molecular clasps, without the need to inquire into how the generated molecular clasps actually works. Therefore, a detailed description of those random mutagenesis coupled with screening methods, which the instant application contains, are sufficient for the purpose of written description.

In fact, claim 1 of the cited U.S. Pat No. 5,988,204 reads:

1. An isolated nucleic acid sequence which encodes a fluorescent indicator, the indicator comprising:
   - a binding protein moiety having an analyte-binding region which binds an analyte and causes the indicator to change conformation upon exposure to the analyte;
   - a donor fluorescent protein moiety covalently coupled to the binding protein moiety; and
   - an acceptor fluorescent protein moiety covalently coupled to the binding protein moiety,
   - wherein the donor moiety and the acceptor moiety change position relative to each other when the analyte binds to the analyte-binding region, altering fluorescence resonance energy transfer between the donor moiety and the acceptor moiety when the donor moiety is excited.

   (emphasis added)

Applicants could not find, in the specification of the '204 patent, how these emphasized functional languages are effectuated, in terms of a detailed molecular mechanism of how the donor and acceptor moieties can "change position relative to each other" (an allosteric effect) upon binding of a ligand / analyte by the acceptor.

The Office Action also suggests that the specification provide no working example outside the YFP / CFP example for the independent claims. Since claims 1, 3-6 are canceled to expedite prosecution, Applicants need not address this issue here.

Finally, the Office Action asserts that the alleged structural complexity, the alleged broad scope, the alleged need to configure the components to work together, the alleged absence of working example, and the alleged failure of the disclosure to set forth structural features of the claimed subject matter, renders a skilled artisan impossible to envision the full scope of the claimed molecular clasp, or "to show that the applicant was in possession of the claimed invention commensurate to its scope." The Office Action further alleges that the described screening methods are insufficient to define a molecular clasp "solely" by its principle functional property, and is simply a wish to know the identity of any molecule with that property (citing *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993) and *Regents of the Univ. of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CAFC 1997)).

Applicants submit that the standard the Office Action seems to be applying here is improper since it corresponds to that of enablement, not written description. In *In re Wilder*, 736 F.2d 1516, 1520 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 1209 (1985), CAFC flatly stated: "The description requirement is found in 35 U.S.C. § 112 and is separate from the enablement requirement of that provision." This position was later affirmed in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562 (Fed. Cir. 1991). See also MPEP 2161. Even if this can be construed to mean that the description of the species molecular clasps are not representative of the broad genus of the inventions claimed in the originally pending independent claims, Applicants submit that there is no need to address this issue here, since independent claims 1 and 3-6 are canceled to expedite prosecution, and since the described single chain antibody embodiments are sufficiently representative of the subgenus claimed in claim 2 and its dependent claims.

Applicants also wish to draw a distinction between the instant case and the cited cases. In *Fiers*, the applicants attempt to claim a DNA sequence based on a method that could lead to the isolation of that sequence, without knowing what the chemical structure (nucleotide sequence) of the DNA claimed. In other words, the applicants there tried to claim a molecule based solely on function, not structure, thus the written description requirement was not met. However, that is not to say that any claim at least partially based on the function of the molecule claimed would

fail to meet the written description requirement. In Example 9 of the "Revised Interim Written Description Guidelines Training Materials," the hypothetical claim is directed to a genus of nucleic acids, all of which must hybridize with SEQ ID NO: 1, and must encode a protein with a specific activity. Since the hypothetical SEQ ID NO: 1 is novel and fully disclosed, and falls within the scope of the hypothetical claim, the single species meets the written description requirement. As to the genus claim, the Guideline further elaborates that "a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus a representative number of species is disclosed...and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention." Thus the conclusion of the Guideline is: The claimed invention is adequately described.

Applicants submit that this is the situation in pending claim 2. Applicants do not attempt to claim a "modular molecular clasp" that is defined solely by its functional characteristic. Rather, the desired functional characteristic is coupled with distinct structural features including various domains. Especially in the pending claims, the MRE comprises single chain antibodies, the skeleton structure of which is well-conserved (otherwise, it would not be a single chain antibody by definition). Although the effector is, and should not be, limiting, the instant specification has described representative species of the effector molecules that could be adapted to use in the claimed invention (see pages 5, 9, 13-20). A similar detailed description of the transducers and MREs can be found in the immediately preceding sections of the specification.

In view of the guidelines recited above, and the arguments presented below, Applicants respectfully submit that the Office Action has failed to fully consider the factual evidence submitted by Applicants in light of the strong presumption due to the disputed terms – all of which were included in the original claims as filed – and has not shown why Applicants' supporting evidence is insufficient. Neither does the Office Action provide documentary evidence or convincing technical reasoning as required by the Guidelines (MPEP 2163.02) to rebut the presumption in favor of the Applicants.

For the reasons presented above, Applicants submit that all pending claims as amended fully comply with the written description requirement. Accordingly, reconsideration and

withdrawal of written description requirement rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph - enablement

Claims 1-3, 5-8, and 10-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a molecular clasp comprising a single chain Ab 1LMK or 1A14 comprising YFP and CFP effector molecules, allegedly does not reasonably provide enablement for the broad scope of any molecular recognition element, and effector and a transducer. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The Office Action attempts to analyze the "Wands factors" in MPEP 2164.01(a), and alleges that the nature of the invention and breadth of the claims are broad, that the state of the art is relatively unpredictable, that Applicants have provided fairly general directions, and concluded that undue experimentation is needed to practice the invention commensurate with the full scope of the claims.

Claims 1 and 3-6 are canceled without prejudice to expedite prosecution. Rejection to these claims are thus rendered moot.

Regarding the Office Action's concern that it might be relatively unpredictable to mutate amino acid residues to achieve a predetermined biological function, Applicants submit that the rejection is largely based on a somewhat narrow, and even biased stand point of *biochemical protein engineering*, rather than the complimentary approach of *random mutagenesis coupled with genetic screening*, as is preferred in the instant application. One simple example may help to illustrate the point.

Temperature sensitive (Ts) mutation exists in many (if not all) proteins where it is desired and has been sought for. A protein with such a Ts mutation retains its biological function at a lower temperature (say, room temperature), while partially or completely loses its function at a higher temperature (say, 37°C). From a biochemical protein engineering point of view, engineering such a protein based on a wild-type protein is nearly a clueless task – there are so

many residues in any given protein, each of which can be 19 other amino acids, and the substitution of each wild-type residue with a different amino acid could have totally unpredictable effects on thermal stability of the resulting mutant protein. All these difficulties would lead to but one conclusion – it cannot be done. Yet in reality, biologists, especially geneticists routinely generate and use such mutations in almost any protein they study. For example, a search in Entrz PubMed (http://www.ncbi.nlm.nih.gov/PubMed/) using the search term "temperature-sensitive" (including quotation marks) retrieved 11,202 publications as of April 3, 2004, with 437 publications in 2000 alone (the year before the filing of the instant application). A random survey of the publications revealed such Ts mutants in a diverse array of proteins including the heat shock protein **hsp10** (Lin et al., FASEB J. 2004 Apr 1, ePublication); **topoisomerase II** (Walker et al., J Biol Chem. 2004 Mar 22 [Epub ahead of print]); **dynamin** (Macleod et al., J Neurosci. 2004 Mar 10;24(10):2496-505); **beta-ketoacyl-acyl carrier protein (ACP) reductase** (Lai and Cronan, J Bacteriol. 2004 Mar;186(6):1869-78); and **alpha2-tubulin** (Weir and Yaffe, Mol Biol Cell. 2004 Apr;15(4):1656-65. Epub 2004 Feb 06), to name just a few.

Part of the reason that geneticists are successful in generating such function-oriented mutations is that their random mutagenesis screen approach *does not* depend on predicting effects of any particular mutations. There is no need to look at the structure or even sequence of the wild-type protein, and to ponder which one of many can or should be substituted with what other amino acid. And there is certainly no need to predict the effects of any of the mutations. In other words, the secret of the random mutagenesis screening is indeed a simple one – generating many (all) mutations one can possibly screen, and pick amongst them the ones that possess the desired function.

However, this is not equivalent of saying that bio-engineering is useless. Although theoretically possible, it is unlikely that random mutagenesis will generate a photosynthesis enzyme from a structural protein such as actin. Rather, bioengineering is quite effective when combined with random mutagenesis. For example, heterologous protein domains with distinct functions can be linked together to generate novel functions in the resulting new protein as a whole. Such novel functions can be further optimized by random mutagenesis. This is the same approach the instant application prefers.

Therefore, even if what Marvin, Brennan, and Richards taught are all true, they do not conflict with the teaching of the instant application, and thus cannot be relied upon as evidence that the teaching of the instant specification is not enabling. Small changes in any individual protein may indeed have unpredictable effects on overall stability or function on *that* individual protein, but such changes on such a protein are merely one of many possibilities in a large scale mutagenesis scheme, and are thus insignificant in the general approach of the random mutagenesis screening.

The Office Action contends that the teaching of the instant application is generic and lack of detail. Applicants submit that this level of detail is all that is needed by a skilled person in the art to carry out the claimed invention. In fact, there are numerous appropriate MREs, transducers, and effectors as exemplified by the instant application, there is no need and unduly burdensome for Applicants to describe the details of constructing each and every combinations of these interchangeable parts in libraries (the general approach of which is arguably the same). For similar reasons, the crystal structure-based modeling is not limiting either, especially given the highly conserved structures of antibody skeletons.

Lastly, the Office Action asserts that to require a skilled artisan to construct and screen libraries, even for the claimed single-chain antibody embodiment would require undue experimentation since "the skilled artisan cannot predict which ligand-antibody interactions will provide a useful change in effector function." Applicants respectfully disagree.

First of all, Applicants reiterates that there is no need to *predict* whether a specific ligand-antibody interaction could provide a useful change in effector function – the purpose of the screening is to *find out* which ligand-antibody interaction can result in such a change.

Secondly, Applicants submit that the amount of experimentation involved in constructing a library of randomly mutagenized candicate molecules for screening, and the actual screening itself is not overly large in view of the relative level of skill in the art (which is high) at the time of filing. In fact, pharmaceutical companies routinely screen billions of molecules, if not more, in identifying potential drug molecules.

Thirdly, the Office Action seems to have confused the "scope enabled by the instant specification," with "what is needed to practice one embodiment within the scope of the claimed invention." The teaching of the instant specification might have enabled a large scope of modular

molecular clasps. However, to determine if *individual* embodiments within such a scope are enabled, a skilled artisan need not try to make *all* embodiments within the scope. For example, if the claim is "a table," when determining if there is undue experimentation, one should not look into how much combined experimentation a skilled artisan need to engage to make all embodiments within the scope, say, a square table, a round table, an oval table, a red table, etc. Rather, one need only to determine the amount of experimentation for each individual embodiment to decide whether that embodiment is enabled. If almost all individual embodiments within the scope are enabled according to this standard, the full scope is enabled, even though the combined amount of experimentation for all embodiments might be "undue." Thus, although there could be many embodiment in the claimed invention, a skilled artisan need to practice all of the embodiments to obtain a specific modular molecular clasp he desires. For example, the skilled artisan could choose only one or two effector molecule(s) (such as GFP or its variants, see Example), an assay for which is typically well-known (such as FRET), and combine it with the library of transducers and MREs. Since the assay, in most cases, can be carried out in large scale or even automation, the amount of work involved is routine in the art and quite manageable.

Finally, even assuming that a skilled artisan might need to conduct a large amount of experimentation (which is itself arguable in the instant case), that does not mean that the experimentation is undue. A case on point in that regard is screening for monoclonal antibodies.

In fact, in view of the CAFC ruling in *In re Wands*, Applicants submit that the scope of the claimed invention is fully enabled for the reasons which follow.

Jack Wands *et al.* claims methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. The broadest method claim on appeal reads:

> 1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
>
> contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
>
> determining the presence of said substance in said sample;
>
> wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

The PTO Board finally rejects the claims on grounds of lack of enablement. Specifically, the sole issue is whether it would require undue experimentation to produce high-affinity IgM monoclonal antibodies with the recited avidity.

The CAFC summarizes the process of making monoclonal antibody, especially the desired IgM Ab in the following paragraphs in its opinion:

> "In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. ... Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.
>
> The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medium in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.
>
> Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody-antigen binding, but does not yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1}." (emphasis added)

Wands made 10 fusions (each fusion is functional equivalent to the generation of a library of candidate modular molecular clasps for screening), the first four were unsuccessful due to technical problems and inexperience, the next 6 fusion before filing and the 11^{th} fusion after filing were all successful. From among the 6 successful fusions, they screened an undisclosed large amount of candidate hybridomas, and obtained 143 so-called "high-binding hybridomas,"

which produce antibodies that bind the antigen (HBsAg) with at least 10,000 cpm in the commercial RIA assay used by Wands. From these 143 hybridomas, they obtained 4 that actually produce IgM monoclonal Abs that fall within the scope of the claim.

Applicants note a striking parallelism between the *Wands* fact pattern and the claimed invention. First of all, *Wands* claims an assay method using a specific kind of antibody with desired functional feature (with a binding affinity constant for the antigen of at least 10^9 M^{-1}. The claimed invention claims a modular molecular clasp with desired functional feature (ligand binding to MRE leads to a detectable change in an activity of the effector). In fact, the subject peptides of the claimed invention is not purely defined by function, but rather defined by function correlating to structure.

Secondly, the Wands method uses IgM, which can be made through a well-known, but seemingly very complicated and tedious process (monoclonal antibody generation) by screening large amounts of candidate antibodies, for a specific subset of antibodies with the desired function. The claimed invention can be made through another well-known, but arguably less complicated process (combinatorial random mutagenesis) by screening large amounts of candidate polynucleotides randomly mutated, for a specific subset of polynucleotides encoding proteins with the desired function (supra). In both processes, although the amount of work may not be trivial, it is by no means undue in their respective arts. To say that Applicants have only generated one specific claimed modular molecular clasp as shown in the Example, and that Applicants have provided insufficient guidance or working examples other than that in the Example, is analogous to say that Wands has only identified four IgM antibodies falling within the scope of the claimed methods, and that Wands have provided no guidance or working examples other than those 4 identified IgM antibodies.

Based on the above argument, Applicants submit that the specification has provided ample working examples that reasonably correlate with the full scope of the claimed invention, a skilled artisan would be able to practice the claimed invention without undue experimentation. Thus, the enablement requirement of 35 U.S.C. 112, first paragraph is met. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. 112, second paragraph

Claim 2, 5-7, 18, 19, 21-33, 35, and 40-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Particularly, the Office Action points out that claim 2 and its dependent claims 23-31 and 40-45 recite the term "said molecular recognition element," which appear to have insufficient antecedent basis for the limitations in the claims. Accordingly, Applicants have amended claim 2 to obviate this rejection. Applicants submit that there is no narrowing of scope in any respect due to these amendments.

Claims 5, 6, 18 and 32 are rejected as being indefinite for reciting the term "derived from." Claims 19, 22-31, and 40-45 are rejected as indefinite insofar as they depend from claims 5, 6, 18, or 32. Without acquiescing in the reasoning of the Office Action, Applicants have amended claims 5, 6, 18, 21, and 32 to clarify the subject matter claimed. Amended claims does not recite "derived." Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 7 is rejected as lacking antecedent basis since it recites "the energy." Applicants submit that "the energy" is an inherent characteristics of ligand binding to MRE. According to MPEP 2173.05(e): "Inherent components of elements recited have antecedent basis in the recitation of the components themselves." Thus reconsideration and withdrawal of this rejection is respectfully requested.

Claim 33 is rejected as allegedly being indefinite, since it is allegedly unclear whether the recited "artificial polypeptide" refers to "the natural occurrence of the polypeptide," or "the mode of synthesis of the polypeptide." Applicants have adopted the Examiner's suggestion and amended claim 33, which amendment is supported by page 11, line 5 of the specification.

Claim 35 is rejected for using trademark name without generic description in the disclosure. Applicants have amended the specification as required by the Examiner to provide generic descriptions of the products under the respective trademarks. Applicants submit that these amendments obviate the rejections and introduce no new matter. Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

Claim rejections under 35 USC §102

The Office Action states that claims 1, 3-5, 8, 15, 18, 24-26, 28, 29, 32, and 38-45 are rejected under 35 USC 102(e) as being anticipated by Tsien et al. (U.S. Pat. No. 5,998, 204).

To expedite prosecution of the remaining claims, Applicants have canceled claims 1, xxx without prejudice. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Regarding claim 3 (and its dependent claims), the Office Action asserts that Tsien teaches that the protein complex might comprise a transducer comprising a pair of polypeptides that form a *noncovalently* bound complex in response to ligand binding. In support of this, the Office Action specifically refers to claims 3 and 8, especially Figure 1 of Tsien and the caption thereto.

However, Applicants are unable to find any disclosure in Tsien that tend to suggest a noncovalent compound. In fact, the term "noncovalent" could not be found anywhere in the specification of Tsien. In Figure 1, the whole construct is clearly one single fusion protein: the donor moiety is *covalently linked* to the binding protein moiety, which is *covalently linked* to the linker moiety, which is *covalently linked* to the target peptide moiety, which is again *covalently linked* to the acceptor moiety. The lower half of Figure 1, which depicts the conformation of the fusion protein upon binding of the analyte, might be a little misleading in that the linker moiety is probably hidden behind the target peptide moiety. This might give rise to the false impression that the donor moiety – binding protein moiety forms one fusion protein, which is then non-covalently bound by the target peptide moiety – acceptor moiety fusion protein. However, nowhere in the specification of Tsien indicates that the linker moiety is broken upon analyte binding. In fact, column 2, lines 4-13 unequivocally indicates that "... the indicator further includes the target peptide moiety and a linker moiety that covalently couples the binding protein and the target peptide moiety...The binding protein moiety can be covalently coupled to the donor fluorescent protein moiety and the target peptide moiety can be covalently coupled to the acceptor fluorescent protein moiety. The indicator can be a single polypeptide" (emphasis added). See also column 7, lines 2-6 ("In one embodiment, depicted in FIG. 1, the acceptor moiety is covalently bonded to a target peptide moiety that also binds to the binding protein moiety and the target peptide moiety is covalently bonded to the binding protein moiety by a linker moiety" emphasis added).

Therefore, there is no teaching in Tsien that explicitly, implicitly, or inherently suggests a non-covalent complex, and Tsien cannot anticipate or render obvious claim 3 and its dependent claims. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action also rejects claim 1 and several dependent claims of claim 1 for being anticipated by one or more of Benito et al., Baird et al., and Zaccolo et al. None of these references are cited as a basis for anticipation of claims 2 and 3 (and their dependent claims).

Since claim 1 is canceled without prejudice, and rejections of dependent claims of claim 1 rely on the alleged anticipation of claim 1, these rejections are rendered moot.

In view of these amendments, Applicant submits that all pending claims are novel. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 102 are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

Date: June 21, 2004

Yu Lu, Ph.D.
Reg. No. 50,306

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050